Remarks

The Examiner maintained the rejection of claims 39-40, 42-44 and 46-60 under 35 U.S.C. 103(a) as being unpatentable over Jang (US 4590062) in view of Khan (US 5656296). Reconsideration is requested.

In the Final Office Action of October 22, 2003, the Examiner argued that:

- it would have been obvious, at the time the invention was made, to vary the amounts of active agent as well as the amounts of wax present in the formulation of Jang,
- it would have been obvious to include, as the active cores of Jang, the particles taught by Khan, and
- one of ordinary skill in the art would have been motivated to perform the changes in the amount of active agent and the amount of wax and other excipients.

Jang teaches tablets produced by compressing a controlled release formulation comprising :

- from 0.01 to 95% of a particulate biologically active agent, and
- from 5 to 99.99% of a controlled and continuous release binder admixture, said binder admixture providing a matrix for the particulate biologically active agent, containing :
  (a) from 0 to 99% of a fatty acid material or neutral lipid powder,
  (b) from 0 to 99% of a wax powder, and
  (c) from 1 to 100% of a hydrophobic carbohydrate polymer powder, e.g. ethyl cellulose.

All components of the formulation of Jang are included as powders or particulates. A **first distinguishing feature** of the present invention is that components are included into the solid shaped article (tablet) in the form of beads (pellets), not powders. As is well known in the art, beads (or pellets) are distinguishable from powders or granules. Beads (pellets) are defined as small, free-flowing, spherical or sphere-like units manufactured by pelletization. Pelletization is an agglomeration process that converts fine powders or granules into beads. As opposed to the process of granulation, the production of beads results in a narrow size-range distribution. The more spherical nature of beads compared to granules provides better flow and reduces segregation due to shape differences. Also, the surface morphology of

beads is optimal for applying a coating, especially a functional coating i.e. a coating able to sustain the biologically active ingredient action.

Jang teaches a production process (dry powder blending) which is readily distinguishable from pelletization and which cannot yield beads as required by claims 39 and 44.

Jang does not teach coating the particulate biologically active agent. A **second distinguishing feature** of the present invention is that biologically active agent beads must be coated. From this requirement there occurs a further complication which has to be solved. A particular problem occurs if the pellets are coated, usually with a polymer film, to yield a controlled release effect, as the tabletting process causes severe damage to the coating, altering the release characteristics from the pellets. This damage is caused by compression pressure which is an essential step in tabletting. This problem is necessarily absent from the formulation of Jang.

Solving the problem of protecting the coating of the pellets during tablet compression would not have been obvious, even though one compressible component of the formulation (wax) may be chemically identical to the corresponding excipient in the formulation of Jang. This is because:

- wax is present in the form of beads (pellets), not powder, and
- the amount of wax must be selected in order to simultaneously achieve a desirable cushioning effect and preventing cracking of the coating, while keeping a controlled release of the biologically active agent.

A selection has to be made within the extremely broad ranges of components taught by Jang. It is not obvious that any solution can be found which allows release of the active agent and simultaneously prevents damage during tabletting compaction. A wax amount in the upper part (99%) of the range of Jang has been found to block release of the biologically active agent, whereas a wax amount in the lower part (5%) of such range has been found ineffective for preventing cracking of the coating during tablet compression. Nothing in Jang suggests

the wax amounts defined in the instant claims, nor that it is even possible to define an amount of wax which achieves both aspects of coating protection and drug release.

Turning next to Khan, Khan teaches dual control release systems, including tablets made by compression, comprising :

(a) a core having 60 to 90% of a drug, and 5 to 40% of an edible material having a melting point from 25 to 100°C which may be a natural wax or a microcrystalline wax, and

(b) a porous coating layer over the core,

the weight ratio of the core to the coating layer being from 94 :6 to 98 :2.

The system of Khan is prepared by melting the edible material and drug to form a molten mixture, cooling and milling the mixture and compressing the milled mixture to form a tablet core, then coating the tablet core with a coating layer aqueous suspension.

A **first distinguishing feature** of the present invention is that Khan does not teach the use of beads, and thus does not teach replacing the powders of Jang with beads. Khan teaches a production process (melting, milling and compressing) which is suggestive of the use of powder components, and certainly does not suggest pelletization. Therefore, Khan can in no way yield beads as required by the instant claims.

Although Khan does teach a coating, a **second distinguishing feature** of the present invention is that the coating is present on the biologically active agent beads (i.e. before compression of the tablet), whereas Khan has the coating on the complete tablet (i.e. after compression). Thus Khan does not teach that a coating on pellets making up the tablets can be protected during the compaction phase. Even a combination of Jang and Khan, i.e. applying the coating of Khan onto the tablet of Jang, would not result in a tablet similar to that of the present invention, but rather a tablet comprising a mixture of wax and powder, formed into a tablet and then coated.

The purpose of the present invention is to prevent cracking of the coating during tabletting while at the same time keeping the desirable controlled release profile of the biologically active ingredient contained in the formulation. The solution to that problem, as defined by the instant claims, is not derivable from a combination of the teachings of Jang and Khan, because both references fail to recognize the importance of the main distinguishing features of the invention, i.e. (1) beads and not powders, (2) the presence of a coating on the beads which is able to sustain the integrity of beads during compaction and (3) that the wax in the amounts claimed does not prevent active agent release.

Thus the combination of Jang and Khan does not make obvious the subject matter of amended claims 39 and 44 or any claim depending therefrom.

The distinguishing features of the present invention result in unexpected advantages which the applicant reserves the right to demonstrate by additional experimental evidence in a supplementary response to the Office Action.

Conclusion

In view of the arguments presented therein, favorable reconsideration in the form of a Notice of Allowance is respectfully requested. Should, for any reason, this application not be allowable, an interview is requested, as the application is a very important case to the assignee.

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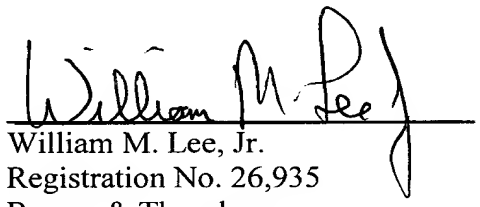
Respectfully submitted,



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